REMARKS

The final Office Action ("Communication") dated July 16, 2002 has been received and reviewed. Claims 1–18 are pending in the application. Claims 19 and 20 were previously canceled. By way of the present communication, claims 2, 5 and 13 have been canceled, claims 1, 6, 11, 14 and 15 have been amended and new claim 21 has been added. Claims 1–4, 6–12 and 14–18 stand rejected. The application is to be amended as previously set forth. All amendments are made without prejudice or disclaimer. Reconsideration is respectfully requested.

1. **Examiner Interview**

Applicants would first like to thank the Office for the courtesy extended applicants and their representative at the interview of October 8, 2002. Many of the issues were clarified and applicants are responding per their understanding of the outcome of the interview. Also, as agreed at the interview, applicants are filing a request for continued examination in response to the office action. As discussed at the interview, applicants are submitting an unsigned Declaration of Lothar Steidler. An executed copy will be provided the Office upon its receipt by the undersigned.

2. **Cancellation of Withdrawn Claims**

Claims 5 and 13 are drawn to a non-elected invention. These claims have been previously withdrawn from consideration and are canceled herein.

3. **Specification**

The abstract of the disclosure stands objected to because of the word "such". Applicants have amended the Abstract to substitute the words "for example" for "such". Accordingly, applicants request that the rejection be withdrawn.

4. **Claim Objections**

Claim 6 has been objected to due to an informality (*i.e.*, missing the word "disease" at the end of the sentence). Claim 6 has been amended as suggested to correct this inadvertent error.

Accordingly, the objection is believed to have been overcome and withdrawal thereof is respectfully requested.

5. **Claim Rejections under 35 U.S.C. § 112, 1st ¶**

Claims 1–4, 6–12 and 14–18 have been rejected under 35 U.S.C. § 112, first paragraph, for assertedly lacking adequate written description.

Specifically, it was thought that the specification provided insufficient guidance and/or evidence for making and/or using the claimed invention embracing one or more of reduction of inflammation by at least 50% and prevention of onset of said inflammation in any subject. The etiology of Inflammatory Bowel Disease (IBD) is poorly understood and, because the nature of the invention was thought to be "gene therapy", the state of the art was considered unpredictable at the time the application was filed. In this light, the invention is stated to provide sufficient guidance only for one skilled in the art to use a recombinant IL-10 producing *Lactococcus* for the reduction of inflammation of colitis, or prevention of colitis, in a mammal deficient for IL-10 by administering a medicament by intraperitoneal injection. Further, it was thought that it would not be apparent to one skilled in the art how to reasonably extrapolate from a mouse to "any subject" without an undue amount of experimentation. Applicants respectfully request reconsideration.

Regarding the possibility of simultaneously reducing and preventing inflammation in the same subject, it is respectfully submitted that inflammatory bowel diseases, whether Ulcerative Colitis or Crohn's Disease, are characterized by chronic inflammation of the intestinal mucosa. *See*, the Papadakis reference at page 289. Such mucosal inflammation may occur in various portions of the intestine, *e.g.*, the caecum, ascending colon, descending colon, transverse colon and the like. A particular mammal may have inflammation in one or more of these intestinal portions but not in others at the time the disease is diagnosed and treatment begins. The results set forth in the specification clearly illustrate that administration of the medicament may both simultaneously reduce inflammation in those areas of the intestine already affected *and* prevent inflammation in other portions of the intestine, *i.e.*, prevent spread of the inflammation. Thus, it is respectfully submitted that reduction and prevention of inflammation may simultaneously take place in the same subject.

Notwithstanding the foregoing, applicants have amended the claims to split the treatment aspect of the invention from the prevention aspect. Specifically, claim 1 now relates to a method of treating IBD, while new claim 21 is directed to a method of preventing it. Accordingly, this aspect of the rejection is believed to be overcome.

With respect to claim 21, some people have a known genetic predisposition (*i.e.*, possess a specific genotype) for developing IBD later in their life. The invention of new claim 21 would prevent development of IBD, if, for example, these people took IL-10-producing bacteria on a regular basis.

Applicants have further amended the claims to identify that the subject being treated is a mammal. As discussed at the interview, the particular mouse model described in the examples is well accepted in the relevant art, and should provide adequate support for the breadth of the claim as now amended. In support of this contention, an article authored by the inventors of the present invention and published in the renowned journal *Science* (*Science* 2000: 1352-1355) was previously submitted with the Office Action Response filed April 17, 2002. It is stated in the abstract thereof that "[t]his approach may lead to better methods for cost-effective and long-term management of IBD *in humans*" (emphasis added). A statement such as this undoubtedly would not be published in a renowned peer-reviewed journal like *Science* if the extrapolation from mice to other mammals was unacceptable to those of skill in the art.

Further, Papadakis et al., *Annu. Rev. Med.*, vol. 51, pp. 289–298, 289 (2000) ("Papadakis") states that the development of animal models of intestinal inflammation to approximate human IBD has expanded our understanding of the pathogenesis of Ulcerative Colitis and Crohn's Disease and has opened new avenues for the development and testing of novel therapeutics. *Id.* at 289. Papadakis also states that more than twenty animal models of intestinal inflammation have been described and provided the opportunity to study the pathology of mucosal inflammation as well as to "test several therapeutic interventions for potential treatment of human disease." *Id.* at 292. Thus, in the context of IBD, the murine model is widely accepted by those of ordinary skill in the art as a model for the treatment of humans and other mammals.

The claims have also been amended to clearly identify that the invention relates to a delivery system and not *ex vivo* gene therapy. In this regard, it has been identified in the claims that the genetically modified bacteria are administered to the subject's intestine.

The Communication states additional enablement concerns regarding claims 1–4, 6–12, and 14–18 with regard to making and/or using a genus of non-invasive bacteria and/or route of delivering recombinant bacteria to a subject and/or using a genus of cytokines to treat IBD. Specifically, it is stated that the specification and the state of the art provide sufficient guidance only for making and using *Lactococcus lactis* in the manner claimed and cannot be expanded to include any non-invasive Gram-positive bacterial strain in the manner asserted. Further, it is stated that while the state of the art and the specification provided sufficient guidance to make and/or use a nucleic acid encoding the IL-10 protein, this enablement, assertedly, could not be expanded to include any cytokine. Finally, it is stated that the state of the art and the specification provide sufficient guidance only for intraperitoneal injection and not for other modes of administration encompassed by the claim language. Applicants respectfully request reconsideration.

Regarding enablement for any cytokine, the cytokine or cytokine-antagonist has been particularly identified to be selected from the group consisting of IL-10 (see, Examples), a soluble TNF receptor, a TNF antagonist, an IL-12 derived p40 homodimer antagonist, and EBV BCRF1. Specific basis for the materials beyond IL-10 can be found in FIGs. 3-5 (soluble TNF receptor/trefoil factor) and paragraph numbers 37 (pages 8-9), 96 and 109 of the application as filed for IL-12 and EBV BCRF1. Literature supporting applicants claims (and cited in the application at paragraphs 96 and 109, respectively) include Rennick et al., *J-Leukoc-Biol.*, 61(4):389-396 (April 1997) (IL-12) and Baer, R. et al., "DNA sequence and expression of the B95-8 Epstein-Barr virus genome", *Nature*, 130:207-211 (1984) (EBV BCRF1).

Regarding enablement for any non-invasive bacteria, as claimed, the present invention relates to the use of a medicament comprising an amount of a cytokine- or cytokine antagonist-producing non-invasive Gram-positive bacterial strain for treating IBD. Particular Gram-positive bacterial strains for which the present invention may be used include *Bacillus subtilis*, *Streptococcus gordonii*, *Staphylococcus xylosus* and *Lactobacillus species*, such as *L. bulgaricus*, *L. salivarius*, *L. casei*, *L.*

helveticus, *L. delbrueckii* and *L. plantarum*. (*See*, specification, para. **[0038]**.) All of the bacterial strains listed above are non-invasive strains. Independent claim 1 has been previously amended to clarify that only non-invasive Gram-positive bacterial strands are intended to be encompassed by the present invention.

As discussed at the interview, applicants respectfully submit that the state of the art does provide sufficient guidance for one skilled in the art to make and/or use a representative number of non-invasive Gram-positive bacteria, such as those listed above, in the method of the present invention. One skilled in the art would be able, without undue experimentation, to extrapolate from the *L. lactis* examples provided by the present invention to other non-invasive Gram-positive bacteria in the method of the present invention. The specification provides ample guidance to a person skilled in the art regarding how to treat a subject with IBD by administering a suitable non-invasive Gram-positive bacterium as a carrier/production item for any cytokine or cytokine antagonist known to affect the prevention or treatment of IBD.

Regarding enablement for modes of administration other than intraperitoneal injection, as discussed at the interview, the actual mode of administration described in the examples was intragastral (*i.e.*, administration of the genetically modified bacteria directly to the stomach). Oral administration in mice has the disadvantage that it is difficult to determine the exact amount of bacteria taken up by the mice whereas this is not the case with intragastric administration. The invention contemplates well known methods of administering the medicament to the intestine (*e.g.*, by administering acid stable bacteria or using, for example, enteric coatings for delivering less acid stable bacteria to the intestine).

In view of the foregoing, applicants request that the rejections be withdrawn

6. **Claim rejections under 35 U.S.C. §112, 2nd ¶**

Claims 1–4, 6–12 and 14–18 were rejected under 35 U.S.C. § 112, 2nd paragraph, as assertedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention.

Specifically, it was thought that the phrase "one or more of reduction of inflammation by at least 50% and prevention of onset of said inflammation" rendered the claims indefinite and it is not apparent how administration of a medicament results in simultaneously reducing inflammation by at least 50% and prevention of onset of inflammation in the same subject. As previously identified, applicants have amended claim1 to split the treatment aspect (claim 1) from the prevention aspect (new claim 21). Accordingly, withdrawal of the rejection is respectfully requested.

Claims 1–4, 6–12 and 14–18 were further rejected under 35 U.S.C. § 112, second paragraph as being vague and indefinite as to what is intended to be encompassed with regard to the phrase "reduction of inflammation". Specifically, it is stated that the claims do not define and particularly point out what type of inflammation is being reduced. Independent claim 1 (from which the remaining rejected claims depend) has been amended herein to recite "reduction of intestinal mucosal inflammation". It is believed that the addition of "intestinal mucosal" adequately defines and particularly points out the type of inflammation reduced by the methods of the present invention. Accordingly, applicants respectfully submit that the rejection based upon use of this phraseology has been rendered moot.

Claims 1–4, 6–12 and 14–18 were further rejected due to lack of antecedent basis for "said inflammation". Specifically, the term "said inflammation" is stated to lack antecedent basis because the claim does not define which type of inflammation is being reduced in the subject. Additionally, it is stated that it is not apparent if the term is referring to IBD or inflammation. By way of the present amendment, the phrase "said inflammation" has been removed from claim 1 which now recites "intestinal mucosal inflammation". Accordingly, applicants submit that the rejection has been overcome and applicants respectfully request withdrawal of this rejection.

7. **WO 96/11277**

International PCT Publication WO 96/11277 was also discussed at the interview. As applicants believe was agreed to at the interview, the publication merely has a generic disclosure with no specific disclosure of the instantly claimed invention. At worst, the reference would be "an obvious to try" reference with respect to the instant claims, which is not the applicable standard. *In*

re O'Farrell, 853 F.2d 894, 903, 7 USPQ2d 1673, 1680-81 (Fed. Cir. 1988). A general incentive does not make obvious a particular result, nor does the existence of techniques by which those efforts might be carried out and the teachings of WO 96/11277, even in combination with the other prior art of record, fail to suggest the claimed invention. Further, nothing in the reference would lead one to the unexpected results obtained by the invention (*see, e.g.*, reduction of intestinal mucosal inflammation by at least 50% as required by independent claim 1 and the claims dependent thereon.)

CONCLUSION

In view of the present amendment and remarks, the remaining claims are believed to be in condition for allowance and an early notice thereof respectfully is solicited. Should the Office determine that additional issues remain which might be resolved by a telephone conference, he respectfully is invited to contact applicants' attorney at the address or telephone number given herein.

Respectfully submitted,

Allen C. Turner
Registration No. 33,041
Attorney for Applicants
TRASK BRITT, PC
P. O. Box 2550
Salt Lake City, Utah 84110-2550

Date: January 16, 2003

Enclosures: Version of Claims with Marking to Show Changes Made
Declaration of Lothar Steidler (unsigned, w/ enclosures)

VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE ABSTRACT:

ABSTRACT

An administration strategy for the delivery at the intestinal mucosa of cytokines or cytokine antagonists, preferably of acid sensitive anti-inflammatory agents, [such as]for example, IL10 and/or soluble TNF receptor via the oral route. Preferably, inoculation occurs along with a suspension of recombinant *Lactococcus lactis* cells, which had been engineered to produce the respective proteins.

IN THE CLAIMS:

The claims have been amended as follows:

1. (Twice Amended) A method of treating inflammatory bowel disease in a ~~subject~~mammal, said method comprising:

administering a medicament comprising an amount of a cytokine- or cytokine antagonist-producing genetically modified non-invasive Gram-positive bacterial strain ~~to said subject~~, wherein the administration of said medicament results in [one or more of] reduction of intestinal mucosal inflammation by at least 50% [and prevention of onset of said inflammation],

wherein said cytokine or cytokine-antagonist is selected from the group consisting of IL-10, a soluble TNF receptor, a TNF antagonist, an IL-12 derived homodimer, and EBV BCRF1.

6. (Amended) The method according to claim 1 wherein the bowel disease is Crohn's Disease.

11. (Twice Amended) The method according to claim ~~2~~1, wherein the cytokine is IL-10 and the non-invasive Gram-positive bacterial strain is a *Lactococcus* species.

14. (Twice Amended) The method according to claim ~~2~~11, wherein the bowel disease is Crohn's ~~disease~~Disease.

15. (Amended) The method according to claim ~~2~~11 wherein the medicament is administered in combination with at least one additional therapeutic agent.